CBER CMC BLA Review Memorandum

BLA STN 125771/0

antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl

Zuben Sauna, SBRBPAS Expert (Biologist)
Daniel Lagasse, Biologist

1. BLA#: STN 125771/0

2. APPPLICANT NAME AND LICENSE NUMBER

Bioverativ Therapeutics Inc., a Sanofi Company

3. PRODUCT NAME/PRODUCT TYPE

a. Nonproprietary / United States Adopted Name (USAN): antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl
b. Proprietary Name: ALTUVIIIO
c. Company or laboratory code: BIVV001; BIIB073; rFVIIIFc-VWF-XTEN
d. Chemical Abstract Service (CAS) registry number: 2252477-42-0
e. International Nonproprietary Name (INN): efanesoctocog alfa

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category: antihemophilic factor (recombinant)
b. Dosage form: lyophilized powder for solution
c. Strength/Potency: single-dose vials containing nominally 250, 500, 750, 1000, 2000, 3000, or 4000 International Units (IU)
d. Route of administration: intravenous use after reconstitution only
e. Indication: for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:
   - Routine prophylaxis to reduce the frequency of bleeding episodes
   - On-demand treatment and control of bleeding episodes
   - Perioperative management of bleeding

5. MAJOR MILESTONES

Receipt Date: 30 June 2022
First Committee Meeting: 21 July 2022, 10:30 AM – 11:30 AM ET
Application Orientation and Dataset Walkthrough Teleconference: 28 July 2022, 10:00 AM - 12:00 PM ET
Filing Meeting: 17 August 2022, 11:00 AM-12:00 PM ET
Mid-Cycle Meeting Teleconference: 26 October 2022, 11:00 AM - 12:00 PM ET
Late-Cycle Meeting Teleconference: 19 December 2022, 10:00 AM - 11:00 AM ET
Reference Product Exclusivity Determination Board Meeting: 10 February 2023, 1:05 PM – 2:00 PM ET
PDUFA Action Date: 28 February 2023

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter

Daniel Lagasse and Zuben Sauna, Office of Tissues and Advanced Therapies (OTAT)/Division of Plasma Protein Therapeutics (DPPT)/Hemostasis Branch (HB)	Drug Substance (Section 3.2.S) Drug Product (Section 3.2.P) Adventitious Agents Safety Evaluation (Section 3.2.A.2) Regional Information (Section 3.2.R) Environmental Analysis (Section 1.12.14) Exclusivity Claim (Section 1.3.5.3) Reports of Bioanalytical and Analytical Methods for Human Studies (Section 5.3.1.4)

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Millie Shah, PharmD, BCPS Center for Drug Evaluation and Research (CDER)/Office of Surveillance and Epidemiology (OSE)/ Office of Medication Error Prevention and Risk Management (OMEPRM)/ Division of Medication Error Prevention and Analysis 2 (DMEPA 2)	human factors validation study report and labeling review	Yes
David Wolloscheck, Ph.D. Center for Devices and Radiological Health (CDRH)/Office of Product Evaluation and Quality (OPEQ)/Office of Health Technology 3 (OHT3)/Division of Drug Delivery, General Hospital & Human Factors (DHT3C)	combination product: use of the vial adapter with the biologic	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
12 May 2022	STN 125771/0	Pre-submission to rolling BLA (part 1 of 2) [non-clinical]
30 June 2022	STN 125771/0.1	Original BLA submission (part 2 of 2) [administrative, clinical, CMC]

18 January 2023	STN 125771/0.24 (response to 13 January 2023 IR)	Updated (i) DS and DP stability data, (ii) proposed 48-month DP shelf-life
27 January 2023	STN 125771/0.28 (response to 20 January 2023 IR)	Comparability protocol clarifications
08 February 2023	STN 125771/0.32 (response to 01 February 2023 IR)	CMC PMCs #1, DS mixing validation report, and leachables
10 February 2023	STN 125771/0.34 (response to 07 February 2023 IR)	Comparability protocol reporting category update
14 February 2023	STN 125771/0.36 (response to 10 February 2023 IR)	CMC PMCs #2, DS process intermediate hold time limits, and (b) (4) method validation report

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & **#**	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
(b) (4)				

One page has been determined to be not releasable: (b)(4)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This review is an assessment of the CMC information in Biologics License Application (BLA), STN 125771/0, submitted by Bioverativ Therapeutics Inc., a Sanofi Company, from a product quality perspective.

The product is antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl; [INN: efanesoctocog alfa], and its proprietary name for the US market will be ALTUVIIIO. The active ingredient in ALTUVIIIO is a recombinant fusion protein consisting of a single chain B-domain deleted (BDD) human Factor VIII (FVIII) covalently linked to the human immunoglobulin G1 (IgG1) Fc domain, the human Von Willebrand Factor (VWF) D'D3 domain, and two XTEN polypeptides (unstructured polypeptides consisting of repeats of six amino acids [glycine, alanine, proline, threonine, serine, glutamic acid]). The Fc, D'D3 domain of VWF, and XTEN polypeptide portions of the molecule are each designed to extend the half-life of the FVIII molecule in plasma.

ALTUVIIIO is indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for (i) Routine prophylaxis to reduce the frequency of bleeding episodes; (ii) On-demand treatment and control of bleeding episodes; and (iii) Perioperative management of bleeding.

The ALTUVIIIO drug product (DP) is a lyophilized powder for reconstitution as a parenteral solution, supplied in single-dose glass vials containing 250, 500, 750, 1000, 2000, 3000, and 4000 International Units (IU). Each vial is reconstituted with a sterile vial adapter reconstitution device and 3 mL sterile Water for Injection (sWFI) in a pre-filled syringe (PFS) prior to administration by intravenous injection.

We herein present a consolidated review of all the CMC/Product Quality information provided by Bioverativ in the original BLA and subsequent amendments submitted in response to the Agency's information requests (IRs). The reviewers found the information provided in the original submission and in amendments as responses to our IRs to be sufficient to support the identity, quality, purity, safety, and potency of the product, ALTUVIIIO.

B. RECOMMENDATION

I. APPROVAL

The CMC (Product Quality) reviewers recommend approval of this BLA under STN 125771/0.

a. List of Drug Substance and Drug Product manufacturing facilities (refer to CTD Section **3.2.S.2.1 Manufacturer(s)** and **3.2.P.3.1 Manufacturer(s)** of this Review Memo for a complete list of manufacturing and testing facilities).

b. Bioverativ provided a comparability protocol (CP) proposing to add (b) (4) at the (b) (4) site as an alternative ALTUVIIIO DP manufacturer for all dosage strengths. As part of establishing the DP manufacturing process on (b) (4) of the (b) (4) site, Bioverativ proposed manufacturing changes and provided a risk-based impact assessment for each proposed change. Bioverativ also proposed a reduced reporting category of Changes Being Effected 30 (CBE-30) for a future manufacturing supplement. The CMC reviewers concluded that in the aggregate the proposed manufacturing changes constitute a major change with the potential to impact the safety and efficacy of the product and recommended that the proposed manufacturing changes be reported in a Prior Approval Supplement (PAS). In STN 125771/0.34 (received 10 February 2023), Bioverativ agreed and changed the CP reporting category to a PAS.

c. There are seven Post-Marketing Commitments (PMCs) and no Post-Marketing Requirements (PMRs), from a CMC (Product Quality) perspective for this BLA. The PMCs are:

In STN 125771/0.32 (received 08 February 2023), Bioverativ proposed four PMCs to:

(i) add an upper limit to the (b) (4) acceptance criteria in the DS specification
(ii) add a test for (b) (4) to the DS specification
(iii) develop a DS specification to control (b) (4) profiling
(iv) include (b) (4) as an identification test for DS release

For each PMC, Bioverativ committed to submit final reports and Module 3 updates by March 29, 2024, and implement DS lot testing starting with the 2024 DS campaign.

In STN 125771/0.34 (received 14 February 2023), Bioverativ proposed three PMCs to:

(i) develop and include a DS release specification to control (b) (4)
(ii) include DP release specifications for total protein and specific activity
(iii) develop and include DP release specifications to control for individual excipients (polysorbate 80, arginine, histidine, calcium, sucrose)

For the (b) (4) DS release specification PMC, Bioverativ committed to submit final reports and Module 3 updates by June 28, 2024, and implement DS lot testing starting with the Q3 2024 campaign batches.
For the total protein and specific activity DP release specification PMC, Bioverativ committed to submit final reports and Module 3 updates by March 29, 2024, and implement DP lot testing starting with the Q2 2024 campaign batches.
For the excipient DP release specification PMC, Bioverativ committed to submit final reports and Module 3 updates by June 28, 2024, and implement DP lot testing starting with the Q3 2024 campaign batches.

d. Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot CBER release would not be required for ALTUVIIIO because it is a well-characterized recombinant product.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Zuben Sauna, PhD / SBRBPAS Expert (Biologist) / OTAT/DPPT/HB	Concur	
Daniel Lagasse, PhD / Biologist / OTAT/DPPT/HB	Concur	
Mahmood Farshid, PhD / Supervisory Biologist (Deputy Division Director) / OTAT/DPPT		
Basil Golding, MD / Supervisory Medical Officer (Division Director) / OTAT/DPPT		

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

(b) (4)

(b) (4)

(b) (4)

39 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The efanesoctocog alfa (BIVV001) DP is a sterile, lyophilized powder for reconstitution for intravenous injection. It is supplied in aseptically filled single-dose vials in seven nominal strengths 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU/vial. The composition of the formulation excipients prior to lyophilization is the same for all dosage strengths. The quantity of the active ingredient, efanesoctocog alfa, varies for each dosage strength. The lyophilized DP is reconstituted with sterile water for injection (sWFI) supplied in a prefilled syringe at a nominal volume of 3 mL.

The composition of the BIVV001 DP is provided in the table below:

Ingredient	Quantity	Concentration	Quality Standard	Function
Efanesoctocog alfa (BIVV001)	(b) (4) (nominal 250 IU/vial) (b) (4) (nominal 500 IU/vial) (b) (4) (nominal 750 IU/vial) (b) (4) (nominal 1000 IU/vial) (b) (4) (nominal 2000 IU/vial) (b) (4) (nominal 3000 IU/vial) (b) (4) (nominal 4000 IU/vial)	Variable	DS release specifications	Active Ingredient
Histidine	(b) (4)	10 mM	(b) (4)	Buffer
Arginine hydrochloride	(b) (4)	250 mM		Stabilizer
Sucrose	(b) (4)	5% (w/v)		Stabilizer
Calcium chloride dihydrate	(b) (4)	5 mM		Stabilizer
Polysorbate 80	(b) (4)	0.05% (w/v)		Stabilizer
Water for injection	3 mL	--		Vehicle
(b) (4)	--	--	--	Process aid

Reviewers' Assessment: *The information provided in Section 3.2.P.1 is in sufficient detail to evaluate the DP. The active ingredient has been discussed in the review of the*

DS. All other components are compendial and typical of those found in the formulation of other recombinant FVIII protein products.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The BIVV001 DP is presented as a sterile lyophilized powder intended for injection in an aseptically filled single-dose vial. Each vial contains one of seven DP strengths from 250 IU to 4000 IU of BIVV001. Please see previous section (**Description and Composition of the Drug Product**) for detailed information on the amounts and concentrations of all components of the DP.

3.2.P.2.1.1 Drug Substance

BIVV001 is a fusion protein comprised of a single chain B-domain deleted (BDD) human FVIII; the Fc domain of human immunoglobulin G1 (IgG1); the FVIII-binding D'D3 domain of human von Willebrand factor (VWF); and 2 XTEN polypeptides. Please see **Section 3.2.S DRUG SUBSTANCE** of this review memo for a detailed description.

3.2.P.2.2 Drug Product

The initial formulation was based on a similar FVIII product licensed to the applicant, Bioverativ, (b) (4)

Systematic formulation development studies were conducted to confirm the appropriateness of the buffer system and excipients to ensure the stability of BIVV001 DP, with modifications to address the unique molecular biology and biochemistry of BIVV001. The excipients used and the justification for their inclusion in the BIVV001 DP formulation are provided below:

i. A buffer system consisting of 10 mM histidine (b) (4) was selected for BIVV001 (b) (4) DP.
ii. Calcium chloride is present in BIVV001 (b) (4) DP at a concentration of 5 mM. Calcium chloride has been shown to stabilize (b) (4) against dissociation.
iii. Arginine hydrochloride is present in the BIVV001 (b) (4) DP at a concentration of 250 mM. Arginine hydrochloride is included in the BIVV001 formulation to mitigate aggregation but is not in the (b) (4) formulation.
iv. Polysorbate 80 is present in the BIVV001 (b) (4) DP at a concentration of 0.05% w/v to stabilize the molecule against physical and interfacial stresses during manufacturing and reconstitution.
v. Sucrose is present in the BIVV001 (b) (4) DP at a concentration of 5% w/v to stabilize the molecule during the freeze-drying process and during long-term storage of BIVV001 (b) (4) DP.

3.2.P.2.2.1 Formulation Development

The formulation development studies and the results which led to the final formulation are summarized below:

1. Buffer (b) (4) system selection:

To identify a suitable buffer (b) (4) for DP stability, (b) (4) were evaluated. Based on their impact on the aggregation and activity of efanesoctocog alfa, the results showed that the lowest level of aggregation was observed in histidine buffers (b) (4) . The same buffer system best preserved the BIVV001 potency over time.

2. Selection of stabilizing excipients

The excipients polysorbate 80, arginine hydrochloride, calcium chloride and sucrose were evaluated to determine the optimal concentration:

i. Polysorbate 80: (b) (4) polysorbate 80 concentrations from (b) (4) were tested on 250 IU dose and (b) (4) polysorbate 80 concentrations from (b) (4) were tested on 4000 IU dose, to determine the optimal concentration in the formulation. Samples were subjected to (b) (4) , and concentration, aggregation, and maintenance of potency were evaluated. Based on these studies a polysorbate 80 concentration of 0.05% was selected.

ii. Arginine: (b) (4) concentrations of arginine hydrochloride from (b) (4) were evaluated for their impact on BIVV001 (b) (4) (b) (4) . This study demonstrated that a concentration of at least 250 mM arginine hydrochloride resulted in the lowest level of (b) (4) (b) (4) . A concentration of 250 mM arginine hydrochloride was selected in the formulation.

iii. Calcium Chloride: (b) (4) concentrations of $CaCl_2$ ((b) (4)) were tested and a short-term stability study was conducted to evaluate the stabilizing impact. The results of this study showed that 5 mM calcium chloride mitigated physical degradation and preserved potency.

iv. Sucrose: (b) (4) levels of sucrose ((b) (4)) were evaluated with respect to the stability of BIVV001. Parameters tested were (b) (4) potency, protein concentration, (b) (4) and residual moisture. The results of these studies showed that 5% sucrose plays an important role as both a cryoprotectant and lyoprotectant by minimizing (b) (4) and maintaining activity.

3.2.P.2.2.2 Overages

No overage of DS or excipient is introduced in the DP.

3.2.P.2.2.3 Physicochemical and Biological Properties

The formulation of the BIVV001 DP is identical to the DS formulation which has been discussed in **Section 3.2.S DRUG SUBSTANCE** of this review.

Reviewers' Assessment: *Adequate information has been provided with respect to the pharmaceutical development of the DP. The BIVV001 DP manufacturing and composition remains unchanged since the introduction of* (b) (4) *for the clinical material. The formulation closely follows that of a similar therapeutic licensed to Bioverativ,* (b) (4)

3.2.P.2.3 Manufacturing Process Development

The BIVV001 DP manufacturing process consists of the following steps:

(b) (4)

Step 5: In-Line Sterile Filtration

Step 6: Aseptic Vial Filling and Partial Stoppering

Step 7: Lyophilization

Step 8: Capping

Step 9: Visual Inspection

Step 10: Bulk Packaging and Storage

For the Phase 1/2a, single dose study (242HA101) and Phase 1, repeat-dose study (242HA102), the DP was provided as a 1000 IU/vial of BIVV001 containing the following excipients: calcium chloride dihydrate, arginine hydrochloride, histidine, polysorbate 80, and sucrose. The phase 1 BIVV001 DP was manufactured from (b) (4), without any dilution.

For the Phase 3 pivotal study (EFC16293), BIVV001 DP is provided as nominal vial strengths ranging from 250 – 4000 IU/vial. The excipients and their respective concentrations remain the same across all vial strengths and is the same as was used in the prior clinical studies. The seven DP strengths for Phase 3 were manufactured following dilution of (b) (4) to respective DP concentrations.

BIVV001 DP formulation and manufacturing process, referenced as (b) (4), has remained unchanged since initiation of the Phase 3 pivotal study, EFC16293. This process is also the one intended for commercial manufacture.

There are minimal changes to the manufacturing steps for the DP. The evolution of the manufacturing process for DS from (b) (4) have been reviewed in **Section 3.2.S.2.6 Manufacturing Process Development** of this review.

Comparability assessment

An assessment was carried out to demonstrate that DP batches manufactured using BIVV001 (b) (4) are comparable. One strength of DP (b) (4) (1000 IU/vial) was manufactured from the BIVV001-(b) (4) and is designated as CL000080 DP or BIVV001-(b) (4). Seven strengths of DP (b) (4) (250, 500, 750, 1000, 2000, 3000, and 4000 IU/vial) were manufactured from BIVV001-(b) (4) and collectively described as DP BIVV001-(b) (4) or BIVV001-(b) (4). Release and characterization tests from BIVV001-(b) (4) DP batches ((b) (4)) were used for assessing comparability. The comparability assessment showed that the BIVV001 DP batches from (b) (4) met the predefined comparability criteria.

Development of the commercial manufacturing process

Laboratory and industrial-scale studies were performed to define the optimal parameters during the development of the commercial manufacturing process. The parameters evaluated and the purpose of these studies are summarized below:

Parameter tested	Purpose
(b) (4)	
Freeze drying	Optimize the lyophilization cycle to reduce cycle time while maintaining critical quality attributes.
Product strength	Perform a comparability assessment (by characterizing aggregation, concentration, and activity) between BIVV001 diluted DS and all strengths of DP.
Shear	Evaluate the impact of shear stress on the critical quality attributes.
Time out of refrigeration	Evaluate the impact of time out of refrigeration holds up to (b) (4) (b) (4) (b) (4) to assess the longer hold times that could be supported.
Moisture	Evaluate the impact of moisture on storage stability by characterizing appearance, reconstitution time, aggregation, and concentration over time.
Material compatibility	Material compatibility study was performed to investigate the sensitivity of BIVV001 when in contact with a range of commonly encountered materials used during the DP manufacture. The study was designed to utilize excessive stress, in the form of elevated temperature, time, and high material surface area, to identify potential sensitivities to process materials.
Photostability	A photostability study was performed at conditions in excess light-exposure stress as that expected under normal processing conditions to identify potential light sensitivity.

The results of these studies confirmed the suitability of the manufacturing process.

Process risk assessments and control strategy

Bioverativ adopted a level 2A risk assessment system. This system ranks and filters individual process parameters to guide the level of process characterization needed prior to process validation. Risk scores were computed for each process parameter, and from these scores, each parameter was classified as high-, moderate- or low-risk in terms of potential impact to product quality and process consistency. Robustness study plans were then created to focus on process parameter requiring additional experimentation to gain understanding of the design space. The process characterization data generated from these studies were used to establish the commercial operating ranges as well as the process action limits.

Then a level 2B risk assessment was performed for DP (250 – 4000 IU/Vial). Operational parameters were classified as either low-, medium-, or high-risk and appropriate risk mitigation measures were recommended.

Based on the results of this risk assessment, parameter classification was performed. The process risk assessments and characterization studies are fully described in the

BLA submission and were used to determine the final control strategy for the DP and classify the controls as critical or non-critical. A full list of the controlled parameters and process controls for the initial commercial process was established and used for BIVV001 DP PPQ manufacturing.

Commercial control strategy for BIVV001 DP manufacture was kept unchanged as compared to the control strategy put in place for PPQ manufacturing.

Extractables and leachables from manufacturing equipment

An evaluation of the safety risks of measured extractables/leachables was carried out on the BIVV001 product filling line ((b) (4)). The filling line for the DP uses a (b) (4) product-contact pathway. The (b) (4) systems are comprised mostly of (b) (4) materials. There is a potential for compounds to leach from product-contact materials during DP processing in the fill/finish lines.

The risk assessment identified four (4) materials of construction that were high risk and required additional extractables/leachables testing. An extractable study was performed, and the maximum quantity of extracted substance was calculated using BIVV001 process inputs and worst-case patient exposure. Assumptions of the risk assessment are as follows: 1) BIVV001 buffer and BIVV001 DP all have a medium extraction capability because they are aqueous solutions, 2) maximum delivery volume per day is (b) (4), 3) worst case length of product contact is (b) (4), and 4) worst case process temperature is (b) (4).

From this assessment only one potential leachable compound ((b) (4)) was calculated to be a possible risk at a level that exceeds the Safety Concern Threshold. (b) (4) is a (b) (4). Due to its low toxicity, (b) (4) is designated as, "*Generally Recognized as Safe*" by the FDA and is present in at least one commercially injectable product (FDA/CDER inactive ingredient Database for Approved Products).

Additionally, elemental impurities were evaluated in accordance with ICH Q3D. No elemental impurities exceeded the Permitted Daily Exposure limit. Based on these assessments, no additional leachable studies or toxicological studies were performed.

3.2.P.2.4 Container Closure System

The BIVV001 DP container closure system consists of the following:

i. (b) (4) vial, (b) (4) borosilicate glass, clear
ii. (b) (4) chlorobutyl gray rubber closure coated with (b) (4) polymer type film on the product contact side, with a cross-linked silicone oil treatment on the non-coated areas
iii. (b) (4) colored aluminum seals with polypropylene (b) (4) (distinct seal color depending on the nominal vial strength).

Bioverativ has provided details of the compatibility and stability studies in **Section 3.2.P.2.6 Compatibility** and **Section 3.2.P.8.1 Stability Summary and Conclusion** of the application. These studies demonstrate that there are no physical or chemical interactions between container-closure and drug that could lead to critical alterations of

drug content, quality, or purity under recommended conditions of handling, shipment, storage, and use of the product.

An assessment of extractables and leachables from the container closure system in the BIVV001 DP was carried out. The container and closure materials used for BIVV001 DP were selected to minimize the risk that substances in quantities sufficient to affect the stability of the preparation or to present a toxicity risk to the patient would leach into the DP. This container closure system meets all requirements outlined in (b) (4) . for the vials and rubber stoppers. The risk is also reduced because the DP is stored as a lyophilized powder. The physicochemical compatibility of reconstituted BIVV001 DP was tested with co-packaged injection components (sWFI syringe, vial adapter) used for reconstitution and administration, as well as with commonly used infusion sets. Results are described in **Section 3.2.P.2.6 Compatibility** of the BLA application.

3.2.P.2.5 Microbiological Attributes

BIVV001, lyophilized powder for injection in vials, complies with the compendial requirements microbiological attributes as prescribed by (b) (4) . As single-dose presentations are provided, no antimicrobial preservative is added. The BIVV001, lyophilized powder for injection in vials, is sterilized by filtration immediately prior to aseptic filling into the primary container closure. Sterility and content of bacterial endotoxins are part of the BIVV001 DP release testing. The maintenance of the container closure integrity (and thereby sterility) is monitored as part of the manufacturing process and during the shelf life of the DP by container closure integrity testing. After filling and closing operation, vials are routinely tested for container closure integrity, using the (b) (4) deterministic method. As part of the stability studies, container closure integrity is also tested over the shelf-life of the product using the probabilistic (b) (4) method or the deterministic (b) (4) method. The operations associated with container closure integrity testing have been validated. Additionally, maintenance of container closure integrity was also tested by (b) (4) in a simulated shipping study.

3.2.P.2.6 Compatibility

Physicochemical compatibility of the reconstituted BIVV001 DP with diluent and the infusion components (i.e., vial, syringes, vial adapter, and infusion sets) was evaluated.

Physicochemical compatibility

A bracketing approach using the lowest and highest dose strengths (250 IU/vial and 4000 IU/vial) was used in the study to evaluate physicochemical compatibility. The following parameters were evaluated in this study:

i. Hold time stability of reconstituted BIVV001 DP and adapter compatibility: The DP was reconstituted with and without vial adapter, stored in the DP glass vial and tested at times, (b) (4) .
ii. Dose verification, in-use stability, and syringe compatibility (pre-infusion): BIVV001 DP was reconstituted with the vial adapter, stored for (b) (4) in the DP glass vials, and then withdrawn in (b) (4) dosing syringes made of polypropylene

(dosing syringe) and glass (3 mL diluent prefilled syringe) and incubated for a further (b) (4) at (b) (4) prior to testing.

iii. In-use stability, and compatibility with IV infusion tubing (post-infusion): BIVV001 DP was reconstituted with vial adapters, stored in the DP glass vial and the polypropylene dosing syringe was used for a "mock-infusion" at the end of (b) (4). In another test, simulated IV administration was performed at (b) (4) at ambient temperature using an infusion pump and (b) (4) and samples were collected post-infusion. Use of infusion pump for this study was to control the flow rates to the slowest possible flow rate to mimic the worst-case condition of maximum contact time of the DP. The infusion for commercial use will be performed without an infusion pump. The duration of the study, including storage time and mock infusion was (b) (4). An intermediate time point at (b) (4) was also evaluated. The (b) (4) and (b) (4) timepoints included equal time in the vial followed by the same incubation time held in the syringe at (b) (4) conditions. For example, the (b) (4) testing consisted in reconstituted material held in the vial for (b) (4) followed by a second (b) (4) incubation in the syringe, followed by infusion. This evaluation is intended to mimic worst-case scenarios associated with home administration.

The tests used (and acceptance criteria) for the evaluations described above were:

Test	Acceptance criterion
Appearance	(b) (4)
(b) (4)	
Protein concentration	
Activity (aPTT)	
(b) (4)	

All samples tested in this study met the acceptance criteria.

Reviewers' Assessment: *The manufacturing process development has been described in sufficient detail by Bioverativ. All steps in the manufacturing process were appropriately evaluated and the compatibility of the BIVV001 DP with storage, reconstitution, and infusion components has been adequately evaluated.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The BIVV001 DP manufacturing sites for the commercial product and their responsibilities are listed below:

(b) (4)

(b) (4)

3.2.P.3.2 Batch Formula

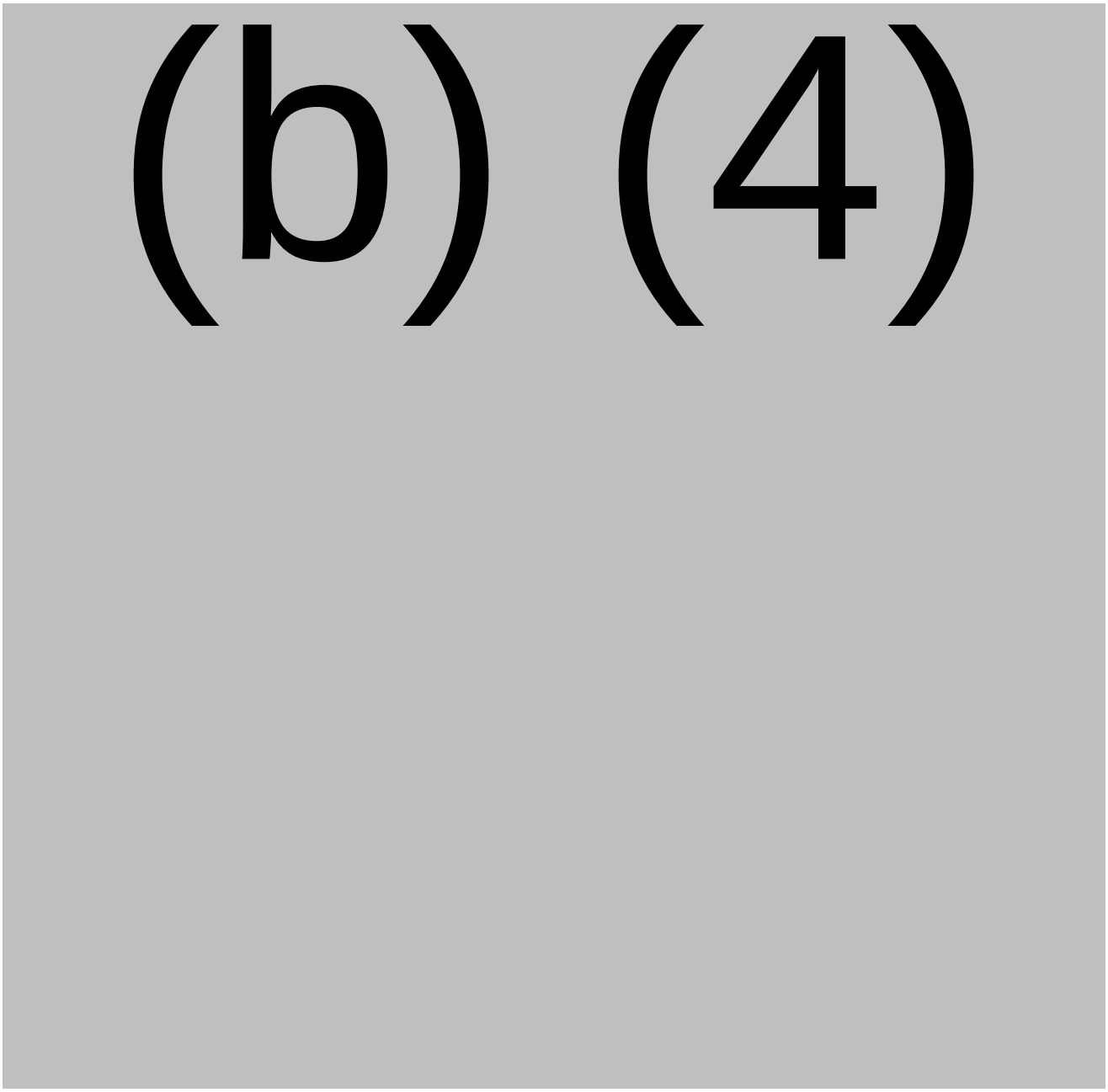
A maximum of (b) (4) batches of BIVV001 (b) (4) to produce a single batch of BIVV001 DP. The quantity of active ingredient varies according to the target vial strength of the DP fill. The concentration of all other components in the formulation are the same across all DP vial strengths. The formulae for the minimum and maximum batch sizes are provided below:

Minimum Batch Formula (b) (4)		
Ingredient	Quantity (per (b) (4))	Quality standard
Efanesoctocog alfa	(b) (4)	
Histidine		
Arginine hydrochloride		
Calcium chloride dihydrate		
Sucrose		
Polysorbate 80		
Maximum Batch Formula ((b) (4) **)**		
Ingredient	Quantity (per 1 (b) (4))	Quality standard
Efanesoctocog alfa	(b) (4)	
Histidine		
Arginine hydrochloride		
Calcium chloride dihydrate		
Sucrose		
Polysorbate 80		

3.2.P.3.3 Description of Manufacturing Process

The manufacturing process for the BIVV001 DP, the in-process controls, and process parameters are summarized below:

(b) (4)



3.2.P.3.4 Controls of Critical Steps and Intermediates
The controls of critical steps and intermediates are provided in the previous section of this review (**Section 3.2.P.3.3 Description of Manufacturing Process**).

3.2.P.3.5 Process Validation and/or Evaluation
Process performance qualification

To demonstrate that the BIVV001 DP manufacturing process consistently produces DP of adequate quality, Bioverativ carried out a PPQ. As part of the PPQ, (b) (4) consecutive batches ((b) (4)) were successfully manufactured between (b) (4) The batch sizes ranged from (b) (4) and

included the lowest, highest, and intermediate strengths (i.e., 250 IU/vial, 1000 IU/vial, and 4000 IU/vial). In-process samples were evaluated, and the results analyzed to demonstrate the consistency and reliability of the manufacturing process. A summary of this manufacturing process validation is provided in the document **P.3.5 Process Performance Qualification summary**, and the results are provided in the document **TR-MS-055533 - DP Process Performance Qualification Report**.

The maximum allowable processing times were demonstrated at-scale as part of the process validation. A list of all the exceptions/deviations and their investigations during the PPQ campaign are provided in the document, **DP Process Performance Qualification Report** in **Section 3.2.P.3.5 Process validation and/or evaluation**.

Efficacy of aseptic processing

The efficacy of aseptic process during the manufacturing of the BIVV001 DP was demonstrated through media fill validation. The details of the aseptic process simulation, the results and evaluation are provided in the document, **P.3.5 Process validation and/or evaluation - Efficacy of Aseptic processing**, in **Section 3.2.P.3.5 Process validation and/or evaluation**.

Shipping validation study

A simulated shipping validation study was conducted to demonstrate that the transportation process does not have detrimental effect on the package integrity and product quality and are detailed in the report, **VV-QUAL-0757641, Simulated Transport Report of BIVV001 Bulk Drug Product**, provided in **Section 3.2.P.3.5 Process validation and/or evaluation**.

The process validation protocols for the real-time transport of BIVV001 finished products for US distribution are also provided in **Section 3.2.P.3.5 Process validation and/or evaluation**.

Reviewers' Assessment: *Section 3.2.P.3 Manufacture is complete and provides details of the manufacturing process. However, the BIVV001 DP PPQ studies did not include* (b) (4) *for variations in critical process parameters, i.e., their PPQ studies were conducted under conditions close to the average as seen in previous campaigns. As manufacturers are not required to perform edge of failure studies, we found the approach acceptable. In our determination sufficient controls have been established to ensure that the manufacturing process can consistently produce high quality product and that deviations (if they occur) can be identified.*

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

All excipients used in the manufacture of BIVV001 DP are compendial grade and are listed below:

Ingredient	Quality standard
Histidine	(b) (4)
Arginine hydrochloride	
Sucrose	
Calcium chloride dihydrate	

Ingredient	Quality standard
Polysorbate 80	(b) (4)
(b) (4)	
Water or Injection	

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

BIVV001 DP excipients are all compendial grade and tested in accordance with compendial procedures.

3.2.P.4.4 Justification of Specifications

All the specifications applied to the compendial excipients are the ones provided by the appropriate monographs.

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal origin were used in the manufacture of the BIVV001 DP.

3.2.P.4.6 Novel Excipient

No novel excipients were used in the manufacture of the BIVV001 DP.

Reviewers' Assessment: *Section 3.2.P.4 describes the Control of Excipients. All excipients are compendial and there are no novel excipients or those of human or animal origin. This section adequately describes the control of excipients.*

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The specifications for the BIVV001 DP are as follows:

Test Attribute	Method	Acceptance criteria	
		Release	Stability
Lyophilized Product, Appearance	(b) (4)	White to off white cake or powder	White to off white cake or powder
Solution, Color	(b) (4)	(b) (4)	(b) (4)
Solution, Clarity & degree of opalescence	(b) (4)	(b) (4)	(b) (4)
Solution, Visible Particulates in Injections	(b) (4)	Essentially free of particles	Essentially free of particles
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Residual Moisture (%)	(b) (4)	(b) (4)	(b) (4)
Reconstitution Time (seconds)	Visual	(b) (4)	(b) (4)

Test Attribute	Method	Acceptance criteria	
		Release	Stability
Identity	One Stage Clotting Assay (aPTT)	Meets Biological Activity Specification	Not tested
	(b) (4)	(b) (4)	(b) (4)
Biological Activity (IU/vial)	One Stage Clotting Assay (aPTT)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purity (%)		(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)
Bacterial Endotoxin (EU/mL)	(b) (4)	250 IU/vial: (b) (4) 500 IU/vial: (b) (4) 750-4000 IU/vial: (b) (4)	
Sterility	(b) (4)	No Growth	Not tested
Container Closure Integrity	(b) (4)	Not tested	Pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Justification of specifications

The distribution of the BIVV001 DP historical release data was used to generate acceptance criteria. The data were evaluated using (b) (4) tests at the (b) (4) confidence level to determine whether tolerance intervals or nonparametric percentiles were applicable for determination of acceptance criteria for the applicable attributes. The tolerance interval values used in justifying specifications indicate that there is (b) (4) confidence that (b) (4) of all future population data will fall above or below the value in the case of 1-sided lower or upper tolerance intervals. Alternatively, the data will fall within the tolerance interval values in the case of 2-sided tolerance intervals. The nonparametric percentiles indicate that (b) (4) of all future population data will fall below the value in the case of 1-sided upper nonparametric percentiles or that the data will fall within the tolerance intervals for 2-sided nonparametric percentiles.

Reviewers' Assessment: *Bioverativ has established a multi-tiered BIVV001 testing strategy (in-process, release, and stability) to ensure that the BIVV001 DP manufacturing process consistently generates DP material with product quality attributes including identity, strength, quality, purity, and potency as they relate to the safety and effectiveness of the BIVV001 product. The majority of the proposed commercial BIVV001 DP release specifications are based on historical DP testing results, so the established specifications will ensure the commercial BIVV001 DP product will be comparable in identity, strength, quality, purity, and potency to the BIVV001 DP material used in clinical studies.*

We noted limitations in Bioverativ's overall DP release strategy compared to similar licensed FVIII products. The BIVV001 DP release control strategy lacks limits for excipients. In addition, total protein and specific activity which are not included as release tests, could be informative about isoforms, fragments, etc. Thus, we obtained PMCs from Bioverativ to add DP release specifications for excipients, total protein, and (b) (4) *in STN 125771/0.32 (received 08 February 2023) and STN 125771/0.34 (received 14 February 2023).*

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

CBER/OCBQ/DBSQC CMC reviewers are responsible for the review of analytical procedures and method validations. The DBSQC reviewers concluded the analytical methods and their validations and/or qualifications reviewed for BIVV001 DP release testing were found to be adequate for their intended use and their rationale is included in an independent review memo.

3.2.P.5.4 Batch Analyses

Batch analyses data are provided in **Section 3.2.P.5.4 Batch analyses** for all BIVV001 DP batches over the development. The following is a list of all BIVV001 DP batches manufactured according to the process that will be used for commercial production (b) (4) :

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.5.5 Characterization of Impurities

The impurities that may arise during manufacture and storage of BIVV001 DP and the control strategies to limit the risk are described below:

Potential process-related impurities		
Impurity	Source	Control strategy
Microbial contamination (bioburden)	Bacterial or fungal contamination (viable)	Bioburden control in (b) (4) Use of (b) (4) Use of pre-sterilized primary container closure components Sterilizing filter validation Aseptic processing (environmental monitoring, validated equipment, and processing area cleaning procedures; use of isolator technology) Verification of sterility and container closure integrity at release or as part of the process and over shelf life
Bacterial endotoxins/ Pyrogens	Bacterial or fungal contamination (viable and non-viable)	Bacterial endotoxins control in (b) (4) Use of (b) (4) Use of pre-sterilized primary container closure components Aseptic processing (environmental monitoring, validated equipment, and processing area cleaning procedures) DP release testing
Particulate matter	Filling equipment	All equipment used at the filling site is qualified 100% visual inspection and rejection of units with particulates after filling Particulate matter testing is performed at DP release and during stability
	Container closure	Containers and closures are compliant with pharmacopeial standards

Leachables	Disposable raw materials	Leachable and extractable assessment of disposable raw materials, including sterilizing filters, at filling site; all materials were determined to be low risk
	Container and closure	Extractable study of container and closure components showed that these pose a minimum risk to product quality
Elemental impurities	Equipment Disposable raw materials Container closure	Testing of potential elemental impurities resulting from equipment, (b) (4), disposable raw materials, including sterilizing filters, at filling site were tested on representative DP batches at each strength (250 - 4000 IU/vial)
Nitrosamines	Raw materials Equipment Manufacturing process, and packaging material	Risk assessment concluded that there is no significant risk that nitrosamines are either present or form in the BIVV001 DP
Potential product-related impurities		
Impurity	Analytical method for detection	Control Strategy
(b) (4)		

3.2.P.6 Reference Standards or Materials

The reference standards are the same as those used for the BIVV001 (b) (4)

3.2.P.7 Container Closure System

The BIVV001 DP is lyophilized in a (b) (4) glass vial. Vials are closed with a (b) (4) chlorobutyl rubber stopper, coated with (b) (4) on the product contact and top surfaces, with a cross-linked silicone oil treatment on the non-coated areas. After the lyophilization process is complete, the stoppered vials are sealed with (b) (4) aluminum seals with a colored polypropylene (b) (4) . A distinct seal cap color is assigned to each nominal vial strength. The details are provided below:

Component	Description of material
Vial	(b) (4) vial, blow back (b) (4) borosilicate glass, clear Compliant with (b) (4)
Stopper	Rubber (b) (4) grey (b) (4) chlorobutyl rubber Coating: (b) (4) -film on the product contact and top surfaces and (b) (4) on non-coated areas Compliant with (b) (4) .

Component	Description of material
	Delivered "ready to sterilize"
Seal (not in contact with the DP)	(b) (4), Aluminum crimping seal Polypropylene (b) (4) cap: Delivered sterilized (by (b) (4)) or ready to sterilize Color codes: • 250 IU/vial (Yellow) • 500 IU/vial (Red) • 750 IU/vial (Garnet) • 1000 IU/vial (Green) • 2000 IU/vial (Royal Blue) • 3000 IU/vial (Mist Grey) • 4000 IU/vial (Orange)

In **Section 3.2.P.7 Container Closure System** of the BLA application, Bioverativ has provided specifications and drawings for the Container Closure System.

Reviewers' Assessment: *The Control of Drug Product described in Section 3.2.P.5 demonstrates that adequate controls are in place to ensure the safety, efficacy, and quality of the BIVV001 DP. Sufficient manufacturing experience and appropriate statistical methods were used to justify the specifications used to ensure the quality of the BIVV001 DP. The container closure system has also been comprehensively assessed to ensure minimal risk.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The stability program for BIVV001 DP followed ICH Guidelines and includes long-term, accelerated, stress, temperature cycling, and photostability studies. The initial shelf-life of the DP is justified by the long-term stability data.

Primary long-term, accelerated, and stress studies were carried out on (b) (4) representative clinical DP (b) (4) batches representing the 250, 500, 1000, 2000, 3000, and 4000 IU/vial presentations.

Supportive stability long-term, accelerated and stress stability studies were performed on (b) (4) representative clinical (b) (4) batches:

- (b) (4) batches each at the lowest and highest strength (250 and 4000 IU/vial). Total (b) (4) batches.
- (b) (4) batch of each intermediate strength (500, 750, 1000, 2000 and 3000 IU/vial). Total (b) (4) batches.

Photostability and temperature cycling studies were performed on (b) (4) batch each of the 250 IU/vial and 4000 IU/vial strengths.

Confirmatory stability studies were performed under long-term, accelerated, and stress storage conditions for the (b) (4) DP batches (250, 1000, and 4000 IU/vial) manufactured in the BIVV001 DP PPQ.

In addition, to the proposed 48-month shelf life for storage at 2 °C to 8 °C; the product may be stored for up to 6 months at room temperature (not to exceed (b) (4) 30 °C) within the 48-month shelf life. The stability data to support this 6-month room temperature storage are generated by including an additional arm in the long-term stability study. This study

to evaluate sequential storage conditions is included in primary, supportive, and confirmatory stability studies.

The stability studies are summarized below:

Conditions	Duration	Testing frequency
Long-term storage condition: +5 °C ± 3 °C	48 months	0, 1, 3, 6, 9, 12, 18, 24, 30, 36 and 48 months
Accelerated storage condition: (b) (4)	12 months	0, 1, 3, 6, 9 and 12 months
Stress storage condition: (b) (4)	6 months	0, 1, 3 and 6 months
Sequential storage conditions: 30 and 42 months at +5 °C ± 3 °C, followed by 6 months at +30 °C (b) (4) (b) (4)	48 months	36 and 48 months

The BIVV001 DP batches used in the stability studies are listed below:

	Type of stability study	Batch Number (Strength)	Batch Size (# vials)	Date of manufacture	Status (Available Long-Term Data)
Primary Stability Study	Long-term and accelerated stability studies	(b) (4) (4000 IU/vial)	(b) (4)		Complete (48 months)
		(b) (4) (250 IU/vial)			Complete (48 months)
		(b) (4) (2000 IU/vial)			Complete (48 months)
		(b) (4) (3000 IU/vial)			Complete (48 months)
		(b) (4) (500 IU/vial)			Complete (48 months)
		(b) (4) (1000 IU/vial)			Complete (48 months)
Supportive Stability Study	Long-term, intermediate, and accelerated stability studies	(b) (4) (4000 IU/vial)			Ongoing (18 months)
		(b) (4) (4000 IU/vial)			Ongoing (18 months)
		(b) (4) (4000 IU/vial)			Ongoing

	Type of stability study	Batch Number (Strength)	Batch Size (# vials)	Date of manufacture	Status (Available Long-Term Data)
					(18 months)
		(b) (4) (250 IU/vial)	(b) (4)		Ongoing (18 months)
		(b) (4) (250 IU/vial)			Ongoing (12 months)
		(b) (4) (250 IU/vial)			Ongoing (12 months)
		(b) (4) (500 IU/vial)			Ongoing (12 months)
		(b) (4) (750 IU/vial)			Ongoing (12 months)
		(b) (4) (1000 IU/vial)			Ongoing (12 months)
		(b) (4) (2000 IU/vial)			Ongoing (12 months)
		(b) (4) (3000 IU/vial)			Ongoing (12 months)
Confirmatory Stability Study	Long-term, intermediate and accelerated stability studies	(b) (4) (250 IU/vial)			Ongoing (9 months)
		(b) (4) (1000 IU/vial)			Ongoing (9 months)
		(b) (4) (4000 IU/vial)			Ongoing (9 months)

The following parameters were evaluated in the stability studies:

i. Appearance, Lyophilized Product
ii. Reconstitution Time
iii. Solution Appearance
iv. (b) (4)
v. Residual Moisture
vi. Purity by (b) (4)
vii. (b) (4) (b) (4)
viii. (b) (4)
ix. One-Stage Clotting Activity (aPTT) Assay

x. Particulates
xi. Container Closure Integrity

Results

The status of the stability studies at the time of submission of the BLA are as follows:

Long-term stability data: The long-term stability data generated to date for the primary batches demonstrate that the results remained within the proposed commercial acceptance criteria (as well as the acceptance criteria in place at the time of testing), through 48 months.

Accelerated stability data: The stability studies for BIVV001 DP stored at the accelerated storage condition of (b) (4) are complete through 12 months. All stability results from these studies met the proposed acceptance criteria.

Stress stability data: The stress stability studies for BIVV001 DP stored at (b) (4) are complete through 6 months. No change as a function of storage time at (b) (4) was observed except for Residual Moisture for two batches (4000 and 1000 IU/vial), with a change of up to (b) (4) over 6 months.

Based upon stability data obtained to date, a 48-month shelf-life at 5 ± 3 °C is proposed for the BIVV001 DP. Additionally, storage of the DP at room temperature (not to exceed 30 °C) for up to 6 months is also supported across all strengths.

Photostability study

A photostability study was performed on (b) (4) supportive stability batches using a bracketing approach ((b) (4) 250 IU/vial and (b) (4) 4000 IU/vial, i.e., the lowest and highest strengths). The DP was packaged in immediate (primary) and marketing (secondary) packaging materials. The immediate (primary) pack is that constituent of the packaging that is in direct contact with the DP and includes any appropriate label representative to what will be used on commercial product. The marketing (secondary) pack is the combination of immediate pack and secondary packaging such as a carton and leaflet. The study was performed as follows:

All results for the exposed samples in both the immediate primary packaging and marketing secondary packaging were comparable to the results from the dark control samples. There was no significant change within the specification range for each assay.

Temperature cycling study

A temperature cycling study was performed on (b) (4) supportive stability DP batches ((b) (4) 250 IU/vial and (b) (4) 4000 IU/vial to bracket all strengths). The purpose of the study is to demonstrate that the BIVV001 DP maintains the characteristics of strength, quality, and purity following exposure to fluctuating temperatures.

The DP vials were exposed to a minimum of (b) (4) temperature cycles at the beginning of the product shelf life (prior to the (b) (4) time point of the long-term stability study for the 250 IU/vial batch and prior to the (b) (4) time point of the long-term stability study for the 4000 IU/vial batch). The temperature cycles were:

	(b) (4)
Temperature (duration)	
(b) (4)	

All results of the temperature cycling study met the acceptance criteria for all parameters tested. The long-term stability study following cycling is ongoing.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Bioverativ commits to complete all the stability studies for the BIVV001 DP and provide updates to the Agency. Annually, if manufactured, Bioverativ commits to placing a minimum of one additional BIVV001 DP batch on long-term stability at 5 °C ± 3 °C, in accordance with ICH stability guidelines. All DP strengths will be placed on stability on a rotating basis. If there are significant changes to the manufacturing process, additional lots of BIVV001 DP will be placed on stability. Bioverativ has also committed to investigate any out of specification or significant atypical trends observed during the stability studies and to report any confirmed out of specification result, or significant adverse trend.

Reviewers' Assessment: *The data presented to date are sufficient to support the requested shelf life of the BIVV001 DP, 48 months from the date of manufacture when stored at 5 ±3 °C in primary packaging and secondary packaging. Data has also been provided to support short term storage (up to 6 months) at room temperature (not to exceed 30 °C).*

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

CBER/OCBQ/Division of Manufacturing and Product Quality (DMPQ) CMC reviewers are responsible for the review of all facilities and equipment information.

3.2.A.2 Adventitious Agents Safety Evaluation

- **Viral Clearance Studies**

Bioverativ based the BIVV001 adventitious agents safety plan on ICH Q5A guidelines. Bioverativ's safety plan includes facility/procedural controls, absence of animal-derived

raw materials, cell bank testing, testing unprocessed bulk harvest samples, and viral clearance studies.

(b) (4)

(b) (4)

Reviewers' Assessment: *The provided adventitious agent safety evaluation and viral clearance study information is acceptable as submitted. Using* (b) (4) *and a* (b) (4) *, Bioverativ has provided documented evidence that the at-scale* (b) (4) *manufacturing process can inactivate and effectively clear enveloped and non-enveloped viruses from representative BIVV001* (b) (4) *material and ensure product safety over the established* (b) (4) *.*

3.2.A.3 Novel Excipients
Not applicable.

3.2.R Regional Information (USA)

- **Executed Batch Records**

In eCTD *Section 3.2.R Regional Information*, Bioverativ provided all BIVV001 DS/DP master and executed batch records for one BIVV001 (b) (4) and (b) (4) BIVV001 DP PPQ batches ((b) (4)).

- **Method Validation Package**

In eCTD *Section 3.2.R Regional Information*, Bioverativ provided a methods validation package summary document. CBER/OCBQ/DBSQC CMC reviewers are responsible for the review of all BIVV001 DS and DP release analytical procedures and method validations, except for (b) (4). The DBSQC reviewers concluded the analytical methods and their validations and/or qualifications reviewed for BIVV001 DS and DP release testing were found to be adequate for their intended use and their rationale is included in an independent review memo. Review and discussion of the BIVV001 DS release (b) (4) is in *Section 3.2.S.4.2 Analytical Procedures* and *3.2.S.4.3 Validation of Analytical Procedures* of this memo.

- **Combination Products**

BIVV001 DP (vial of lyophilized powder for reconstitution) is co-packaged as a biologic-device combination product with a vial adapter, a plunger rod, and a 3 mL diluent (sterile water for injection) pre-filled syringe (PFS).

The Center for Devices and Radiological Health (CDRH), Office of Product Evaluation and Quality (OPEQ), Office of Health Technology 3 (OHT3), Division of Drug Delivery, General Hospital & Human Factors (DHT3C) evaluated the vial adapter [Closed System Transfer Device (CSTD)] for use with the biologic BIVV001 (under an inter-center consult, ICCR# 00868592). The CSTD, a Mixject dispensing pin, received 510(k) clearance from CDRH under (b) (4) The CDRH reviewer had no specific concerns regarding the use of the (b) (4) product with the biologic from a device perspective. The CDRH review did not evaluate the product quality after use with the device (biologic compatibility).

The Center for Drug Evaluation and Research (CDER), Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis 2 (DMEPA 2) evaluated the human factors (HF) validation study report and the draft *Instructions for*

Use (IFU). The DMEPA2 reviewer concluded (i) the human factors validation study adequately evaluated user interactions with the product user interface, (ii) all critical tasks that may result in harm (including serious harm) to the patient or user are identified and evaluated in the HF study, and (iii) the risk control measures are generally effective. The DMEPA2 consult reviewer provided recommendations for the labeling (*Instructions for Use* and *Prescribing Information*) to address certain use errors, use difficulties, or close calls observed with critical tasks in the HF study. The DMEPA2 consult review also identified the residual risk of air embolism if the user does not remove air from the syringe or if the task is not performed correctly. The DMEPA review concluded the user interface does not appear to contribute to use errors or close calls, therefore did not provide specific recommendations to address the risk of air embolism, however the review recommended CBER take into consideration the residual risk of air embolism as part of the benefit – risk evaluation for the proposed product.

Reviewers' Assessment: *The information provided in eCTD Section 3.2.R Regional Information – Medical Devices is acceptable as submitted. Bioverativ provided adequate descriptions for each component of the co-packaged biologic-device combination product.*

We requested a consult review from CDRH (ICCR# 00868592) to evaluate whether the device components of the co-packaged combination product are compatible and suitable for safe and effective reconstitution and administration of antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl drug product to hemophilia A patients. The CDRH consult review provided feedback that they have no concerns regarding the use of the vial adapter with the biologic, pending CBER's evaluation of biologic compatibility with the device. The physicochemical compatibility of reconstituted BIVV001 DP is evaluated under Section 3.2.P.2.6 Compatibility of this review memo.

We requested a consult review from CDER (ICCR# 00868533) to assess whether the human factors engineering studies adequately evaluate user interactions with the product user interface, identify critical tasks that may result in serious harm to the patient or user, and evaluate the effectiveness of risk control measures. The CDER consult review provided recommendations to revise the Instructions for Use and Prescribing Information in our labeling review to address areas of vulnerability that may lead to medication errors.

- **Comparability Protocols**

In eCTD *Section 3.2.R Regional Information*, Bioverativ provided a comparability protocol (CP) (document# VV-QUAL-0740975) proposing to add (b) (4) at the (b) (4) as an alternative BIVV001 DP manufacturer for all dosage strengths. Bioverativ proposes to assess the comparability of BIVV001 DP manufactured at (b) (4) with BIVV001 DP manufactured at (b) (4) using a (b) (4) PPQ approach ((b) (4) PPQ batches, including 250 IU, 1000 IU, 4000 IU, and 250 IU batches to validate all dosage strengths) based on biochemical properties of DP release and characterization testing.

The QC release testing site ((b) (4)) will remain the same for both BIVV001 DP manufacturing sites. The identification by (b) (4) and in-process test ((b) (4)) analytical methods will be transferred to the (b) (4) site.

As part of establishing the BIVV001 DP manufacturing process on (b) (4) of the (b) (4) site, Bioverativ proposes several changes. Bioverativ provided risk-based impact assessments for each proposed change. The proposed manufacturing changes and studies to support the change are detailed as follows:

Container closure system

Change from (b) (4) borosilicate glass vial ((b) (4)) to (b) (4) borosilicate glass vial containing internal hydrophobic silicone coating to product contact area ((b) (4)). (b) (4) applies the uniform hydrophobic coating using (b) (4) to form a covalent bond and avoid free silicone. Based on development studies, Bioverativ concluded the proposed change will improve product aesthetics by reducing product fogging. Bioverativ does not propose any changes to the (b) (4) chlorobutyl rubber stoppers or aluminum vial seals. Initial development studies support no impact to product quality with vial change. Bioverativ proposes the following validation studies: (i) extractables and leachables testing for (b) (4) vial; (ii) demonstrate vial suitability with engineering and PPQ batch data packages; (iii) 100% visual inspection and defect library to be implemented for new vial.

Process equipment

Change from thaw bath that can accommodate (b) (4) per run ((b) (4)) to thaw bath that can accommodate up to (b) (4) per run ((b) (4)). Bioverativ proposes the following validation studies: (i) develop process for thaw baths and thawing process at (b) (4); (ii) demonstrate thaw bath capability with engineering and PPQ batch data packages.

Change from (b) (4) Single-Use Technology (SUT) process ((b) (4)) to (b) (4) SUT process ((b) (4)). The materials used to construct the (b) (4) SUT assemblies used for formulation buffer preparation, mixing, and (b) (4) will not change, only the maximum capacity. A development shear study at worse case conditions demonstrated no impact on CQA. Bioverativ proposes the following validation studies: (i) mixing and dilution studies at large scale with buffer to define mixing parameters for buffer compounding and pooling/dilution steps using (b) (4) SUT; (ii) demonstrate SUT capability with engineering and PPQ batch data packages.

Change from (b) (4). Based on development studies, Bioverativ does not propose to change the lyophilization cycle despite changes to the container closure system and process equipment scale. Bioverativ proposes the following validation studies: (i)

engineering batch and three PPQ batches to be tested for CQA and characterization testing to demonstrate the batch size increase at (b) (4) is comparable to (b) (4) process.

Manufacturing process

(b) (4)

(b) (4)

Reviewers' Assessment: *Bioverativ provided a CP describing a proposed manufacturing change to add* (b) (4) *as an alternative BIVV001 DP manufacturer. Bioverativ also summarized the risks to product quality associated with the change and proposed validation studies to understand the changes and mitigate the risks to product quality. The CP describes validation studies to support the manufacturing changes and an at-scale* (b) (4) *PPQ study design. Bioverativ plans to assess biochemical comparability between BIVV001 DP manufactured by* (b) (4) *and* (b) (4) *through DP release and characterization testing. The CP describes a plan to submit a post-licensure supplement with a reduced reporting category of Changes-Being-Effected – 30 Days (CBE30).*
We requested clarification on (i) the proposed BIVV001 DP characterization testing, and acceptance criteria used to support product comparability, (ii) the number of PPQ batches to be manufactured, and if they will be consecutive batches (iii) the proposed (b) (4) *strategy. We also provided a recommendation that a* (b) (4) *PPQ batches be placed in the stability study under long-term, accelerated, and stressed storage conditions. The information provided in Bioverativ's 27 January 2023 response was acceptable as Bioverativ clarified (i) the proposed DP characterization testing and acceptance criteria, (ii) the PPQ* (b) (4) *strategy, and (iii) the number of batches included in the stability studies.*
Bioverativ has provided a risk assessment for each individual proposed manufacturing change in the CP. However, in the aggregate, the proposed manufacturing changes (vial, filters, filling, lyophilizer) constitute a major change with the potential to impact the identity, strength, quality, purity, or potency of the product as they may relate to its safety or effectiveness. Thus, we don't agree with Bioverativ's proposal for a reduced reporting category of CBE30. The proposed change should be reported in a Prior Approval Supplement (PAS). We recommended that the proposed manufacturing

changes be reported in a PAS. In STN 125771/0.34 (received 10 February 2023), Bioverativ agreed and changed the CP reporting category to a PAS.

Other eCTD Modules
Module 1

A. Environmental Assessment or Claim of Categorical Exclusion
In eCTD *Section 1.12.14 Environmental Analysis*, Bioverativ claims categorical exclusion from preparation of an environmental assessment for BIVV001 under 21 CFR 25.31(c), as the BIVV001 product is comprised of naturally occurring amino acids.

Reviewers' Assessment: *Bioverativ's claim for categorical exclusion from preparing an environmental assessment is valid as BIVV001 is comprised of naturally occurring amino acids, it is unlikely that approval of this product would significantly alter the concentration or distribution of proteins, product metabolites, or degradation products in the environment.*

B. Reference Product Designation Request
In eCTD *Section 1.3.5.3 Exclusivity Claim*, Bioverativ requests a determination of first licensure and reference product exclusivity for BIVV001.

Reviewers' Assessment: *The provided reference product designation information is acceptable as submitted. From a CMC (Product Quality) perspective, we recommend a reference product exclusivity period for BIVV001 (pending licensure).* (b) (4) *structural differences distinguish BIVV001 from* (b) (4) (b) (4) *an enhanced half-life FVIII product licensed to Bioverativ. The final determination of product exclusivity will be made by the CBER Reference Product Exclusivity Determination Board (RPEDB).*

C. Labeling Review
Full Prescribing Information (PI):
In eCTD *Section 1.14 Draft Labeling*, Bioverativ provided draft *Prescribing Information* (PI) and *Instructions for Use* (IFU) documents. We reviewed the CMC-related information from a Product Quality perspective. Our proposed edits and comments were communicated to Bioverativ by the Regulatory Project Manager on 20 January 2023.

Carton and Container Label:
In eCTD *Section 1.14 Draft Labeling*, Bioverativ provided draft vial labels, carton labels, and syringe label information. We reviewed the CMC-related information from a Product Quality perspective. Our proposed edits and comments were communicated to Bioverativ by the Regulatory Project Manager on 20 January 2023.

Modules 4 and 5
Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

In eCTD *Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies*, Bioverativ provided method validation reports for the immunogenicity (neutralizing and binding anti-drug antibodies (ADAs)) and BIVV001 plasma activity (one-stage clotting and chromogenic) bioanalytical assays used for human studies during clinical development.

Immunogenicity assay method validations

Detection of inhibitors/neutralizing ADAs

The detection of FVIII inhibitors in human sodium citrate plasma using a One-Stage Clot (b) (4) Bethesda Assay method [ESO-AUR-CT-TEC-SOP-0007] was validated using (b) (4) as the positive control (validation study# VAL-2010-010-001). The validation study also assessed BIVV001 drug tolerance in the assay [following (b) (4) (b) (4)

Detection of binding ADAs

(b) (4)

The detection of anti-BIVV001 antibodies in (b) (4) plasma using a bridging (b) (4) was validated using (b) (4) as the positive control (validation study# 8374-746).

The detection of anti-D'D3 VWF antibodies in (b) (4) plasma using an (b) (4) was validated using (b) (4) as the positive control (validation study # 186548).

The detection of anti-XTEN antibodies in (b) (4) plasma using an (b) (4) was validated using (b) (4) as the positive control (validation study # 186552).

BIVV001 activity assay method validations

The quantitative measurement of BIVV001 activity in (b) (4) citrate plasma using (b) (4) on the (b) (4) was validated within the range of (b) (4) (validation study # MVR-CT-2016-010-001).

The quantitative measurement of BIVV001 activity in (b) (4) plasma using One-Stage Clot Assay (APTT) with (b) (4) on the (b) (4) was validated within the range of (b) (4) (validation study# MVR-CT-2017-007-002).

Reviewers' Assessment: *The provided immunogenicity (neutralizing and binding ADAs) and BIVV001 plasma activity (one-stage clotting and chromogenic) method validations are acceptable as submitted.*

The immunogenicity assay validation study results demonstrate that the methods have the appropriate specificity, accuracy, precision, range, and drug tolerance level to be suitable for their intended use to detect BIVV001 neutralizing and binding ADAs in (b) (4) *plasma during clinical studies. Bioverativ implemented a multi-tiered approach for the detection and characterization of binding ADAs to the different components of BIV001.*

The BIVV001 plasma activity assay validation study results demonstrate that the methods (one-stage clotting and chromogenic) have the appropriate accuracy, precision, selectivity, linearity, assay interference, and sample stability at storage and working conditions to be suitable for their intended use to quantify BIVV001 activity in (b) (4) *plasma during clinical studies.*